PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 October 2000 (19.10.00)	
International application No. PCT/EP00/01553	**Applicant's or agent's file reference** L/VK98/SGK/2
International filing date (day/month/year) 24 February 2000 (24.02.00)	**Priority date** (day/month/year) 24 February 1999 (24.02.99)
Applicant ALBERTO, Roger, Ariel et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 September 2000 (18.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

09/913788

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
L/WV96/ems/1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01553	24/02/2000	24/02/1999
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant MALLINCKRODT INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/09/2000	21.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pilling, S Telephone No. +49 89 2399 8461

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01553

I. Basis of th r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-14	as originally filed				

Claims, No.:

1-8	as received on	11/04/2001	with letter of	10/04/2001	

Drawings, sheets:

1/7-7/7	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,8
	No:	Claims	1-6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
s e separate sheet

R It m V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statem nt

1. The present application relates to treatment/diagnosis of tumours/malignancies using molecules comprising (i) a tumour seeking biomolecule coupled to (ii) an intercalating moiety complexed to a metal.

2. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D10 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

3. With reference to the definition in present Claim 1 of "*molecules that are taken up by the cell*", it is noted that the present specification fails to describe any specific modification to the present molecules which facilitate uptake of said molecules by any cell(s). Furthermore, since the present examples of DNA strand breakage appear to have been carried out using a free plasmid model (see Example 2) there is no clear evidence in the present specification to show that the present molecules would in fact be taken up by any cell(s). Hence, even if it accepted that the present molecules are taken up by cells then it appears likely that this would occur via a non specific process involving binding of the molecules to the cell followed by endocytosis. This non-specific process would appear equally likely to occur with the molecules described in each of documents D1 to D7 which comprise a preferred biomolecule according to present Claim 2, *i.e.* antibodies, and preferred intercalating agents as defined in present Claim 4, *i.e.* porphyrins, phenanthrolines, acridine or anthracyclines. Moreover, it is also noted that the definition in Claim 1 that "*molecules that are taken up by the cell*" is unclear since no particular cell or type of cells are defined (see below). Hence the aforementioned definition in Claim 1 cannot be relied upon to distinguish the subject matter of the present claims from the disclosure of each of documents D1 to D7 and these documents are considered to be novelty destroying in respect of Claims 1 to 6 as follows;

   Document D1 (Bhalgat) describes diagnosis and therapy of tumours using conjugates comprising an anti-renal cell carcinoma antibody and porphyrin-

copper-67 complex.

Documents D2 (Fawwaz) D3 (Mercer-Smith) D4 (Lewis) and D5 (US-A-5171749) each provide further disclosures of porphyrin-antitumour conjugates and their use to target radioactive manganese/copper to tumour cells for purposes of diagnosis or therapy.

Document D6 (WO-A-93/21957) describes therapeutic and diagnostic immunoreagents comprising a metal radionuclide ion, a complexing agent and an immunoreactive group covalently bonded to said complexing agent. The complexing agents described in D6 include phenanthrolines (*cf.* present Claim 4) and the immunoreactive groups include anti-tumour antibodies.

Document D7 (US-A-5759514) discloses treatment of tumours using a conjugate comprising a DNA intercalating portion, *e.g.* acridine or anthracyclines complexed with a radioactive metal *e.g.* rhodium or bismuth (see Claim 2 therein) and a tumour cell targeting protein, *e.g.* an anti-tumour antibody.

4. Thus, the subject matter of Claims 1 to 6 is not new in view of the disclosures of each of documents D1 to D7 (Article 33(2) PCT).

5. None of the documents discloses molecules having the general structural formulae shown in either Figure 1 or Figure 2. Thus, the subject matter of Claims 7 and 8 is new (Article 33(2) PCT).

6. The following comments are however relevant to lack of inventive step of Claims 7 and 8; Figures 1 and 2 appear to depict conjugates comprising a tumour targeting peptide moiety and an intercalating moiety that have been radiolabelled with technetium using the fac-$[Tc(CO)_3]$ moiety described in document D10 (EP-A-0879505). It appears however, in view of the teaching of documents D1 to D7 that radiolabelling of conjugates comprising a tumour targeting peptide moiety and an intercalating moiety is wholly conventional. Hence, there is considered to be no invention in using the radiolabelling process of document D10 to radiolabel such conjugates as defined in present Claims 7 and 8. In this regard, the method of document D10 is explicitly disclosed to be useful in making therapeutic and/or

diagnostic compositions.

7. Thus, the subject matter of Claims 7 and 8 is not inventive in view of the disclosures of each of documents D1 to D7 when considered in combination with the disclosure of document D10 (Article 33(3) PCT).

Re Item VIII
Certain observations on the international application

8. The reference in Claim 1 to *"molecules that are taken up by the cell"* is considered to be unclear since no particular cell or type of cell is indicated (Article 6 PCT).

INTERNATIONAL SEARCH REPORT

Internat: Application No
PCT/EP 00/01553

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61K51/10 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BHALGAT M K ET AL: "Preparation and biodistribution of copper-67-labeled porphyrins and porphyrin -A6H immunoconjugates." NUCLEAR MEDICINE AND BIOLOGY, vol. 24, no. 2, February 1997 (1997-02), pages 179-185, XP000682959	1-6,9-12
Y	abstract	7,8

X	FAWWAZ, R. A. ET AL: "The use of a porphyrin bifunctional chelator for labeling of a monoclonal antibody with radioactive manganese" JOURNAL OF NUCLEAR MEDICINE: PROCEEDINGS OF THE 36TH ANNUAL MEETING, vol. 30, 1989, pages 935-936, XP000915982	1-6,9-12
Y	abstract	7,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2000	18/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pilling, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 00/01553

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MERCER-SMITH J A ET AL: "The biodistribution of radiocopper-labeled compounds." ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1989) 258 103-21. , vol. 258, 1989, pages 103-121, XP000916022	1-6,9-12
Y	abstract	7,8
X	LEWIS D ET AL: "The cytotoxicity of copper-67 porphyrin-antibody conjugates to a colon carcinoma cell line" ABSTRACTS OF PAPERS AMERICAN CHEMICAL SOCIETY, vol. 202, 25 - 30 August 1991, page Biot 168 XP000916021	1-6,9-12
Y	abstract	7,8
X	US 5 171 749 A (LEVY JULIA G ET AL) 15 December 1992 (1992-12-15)	1-6,9-12
Y	column 4, line 13 -column 4, line 27; example 5	7,8
X	WO 93 21957 A (STERLING WINTHROP INC) 11 November 1993 (1993-11-11)	1-6,9-12
Y	page 6, line 3 - line 10	7,8
X	US 5 759 514 A (MATTES M JULES) 2 June 1998 (1998-06-02) column 2, line 22 -column 2, line 61	1-6,9-12
X	PIMM M V ET AL: "Biodistribution and tumour localisation of a daunomycin-monoclonal antibody conjugate in nude mice with human tumour xenografts." CANCER IMMUNOLOGY, IMMUNOTHERAPY , vol. 27, no. 3, 1988, pages 267-271, XP000915990 abstract	1-6,9-12
X	TRAIL, P A: "Site directed delivery of anthracyclines for treatment of cancer" DRUG DEVELOPMENT RESEARCH, vol. 34, no. 2, February 1995 (1995-02), pages 196-209, XP000916019 abstract	1-6,9-12
Y	EP 0 879 606 A (SCHERRER INST PAUL) 25 November 1998 (1998-11-25) cited in the application page 2, line 25 - line 33; example 3	7,8

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/EP 00/01553

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5171749 A	15-12-1992	US 4883790 A	28-11-1989
		US 4920143 A	24-04-1990
		US 5399583 A	21-03-1995
		US 5283255 A	01-02-1994
		AT 104859 T	15-05-1994
		AU 618725 B	09-01-1992
		AU 1038888 A	21-07-1988
		CA 1333442 A	06-12-1994
		DE 3889231 D	01-06-1994
		DE 3889231 T	11-08-1994
		EP 0276121 A	27-07-1988
		ES 2055735 T	01-09-1994
		JP 1999536 C	08-12-1995
		JP 6008319 B	02-02-1994
		JP 63277700 A	15-11-1988
		JP 2835294 B	14-12-1998
		JP 7258262 A	09-10-1995
		MX 9203250 A	31-07-1992
		US 5095030 A	10-03-1992
		AT 127696 T	15-09-1995
		AU 638675 B	08-07-1993
		AU 3825889 A	08-02-1990
		DE 68924215 D	19-10-1995
		DE 68924215 T	15-02-1996
		EP 0352076 A	24-01-1990
		EP 0641796 A	08-03-1995
		ES 2080745 T	16-02-1996
		GR 3017426 T	31-12-1995
		JP 2149519 A	08-06-1990
		JP 7080887 B	30-08-1995
		NO 179410 B	24-06-1996
WO 9321957 A	11-11-1993	CA 2135059 A	11-11-1993
		AU 2316192 A	29-11-1993
		BR 9207126 A	29-08-1995
		EP 0639083 A	22-02-1995
		FI 945194 A	04-01-1995
		JP 7506667 T	20-07-1995
		NO 944182 A	21-12-1994
		RU 2122431 C	27-11-1998
US 5759514 A	02-06-1998	AU 2284595 A	29-11-1995
		CA 2189051 A	09-11-1995
		EP 0757559 A	12-02-1997
		JP 10503478 T	31-03-1998
		WO 9529707 A	09-11-1995
EP 0879606 A	25-11-1998	AU 7141398 A	24-11-1998
		NO 995160 A	13-12-1999
		WO 9848848 A	05-11-1998

CLAIMS

1. Molecules for treatment and diagnosis of tumors and malignancies, comprising a tumor seeking biomolecule, which is coupled to an intercalating moiety, which is capable of complexing a metal, which metal is preferably a radioactive metal.

2. Molecules as claimed in claim 1 wherein the biomolecule is selected from the group consisting of somatostatin-, neurotensin-, bombesin-receptor binding molecules, antibodies, penetratines™, and molecules binding to the GPIIb/IIIa receptors.

3. Molecules as claimed in claims 1 and 2 wherein the intercalating agent is an aromatic molecule with an intercalative binding affinity for double-stranded DNA.

4. Molecules as claimed in claim 3, wherein the intercalating agent is selected from the group consisting of acridine, porphyrin, ellipticine, phenantroline, carbazole, benzimidazole or compounds with known cytostatic activity (antibiotics) from the class of tetracyclines (anthracyclines), such as daunorubicine, epirubicine or mixoxantrone.

5. Molecules as claimed in claims 1-4, wherein the radioactive metal is a γ-emitting nuclide.

6. Molecules as claimed in claim 5, wherein the radioactive metal is selected from the group consisting of Tc-99m, Re-186, Re-188 and Mn.

7. Molecules as claimed in claims 1-6 having the general structural formula as given in Fig. 2.

8. Molecule as claimed in claims 1-7, having any one of the structures as shown in Fig. 1.

9. Molecules as claimed in claims 1-8 for use as or in a therapeutic or diagnostic agent for treating or diagnosing tumors or malignancies.

10. Use of molecules as claimed in claims 1-8 for the preparation of a therapeutic or diagnostic agent for treating or diagnosing cancer tumors or malignancies.

11. Therapeutical composition, comprising one or more molecules as claimed in claims 1-8 and one or more suitable excipients.

12. Diagnostic composition, comprising one or more molecules as claimed in claims 1-8 in a suitable carrier.